1615
#10
YC

PATENT 8-21-03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:
Nam Joong KIM et al.

Group Art Unit: 1615 **HAND-CARRY**

Application No.: 09/926,590

Examiner: Liliana Di Nola Baron

Filed: November 21, 2001

Attorney Dkt. No.: P67297US0

For: A SOMATOTROPIN COMPOSITION WITH IMPROVED SYRINGEABILITY

REQUEST FOR RECONSIDERATION

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Responsive to the Office Action (Paper No. 9) of June 18, 2003, favorable reconsideration and allowance of Applicants' claims are respectfully requested in view of the following comments and evidence.

The rejection of claims 15 to 18, 21, 22 and 27 "under 35 U.S.C. 102(b) as being anticipated by U.S. Patent 5,520,927" (Kim) is respectfully traversed.

Claim 15 expressly calls for a composition which consists of somatotropin, a lipid-soluble vitamin, and a pharmaceutically acceptable lubricant. No such composition is found in Kim, all of whose compositions require at least some other component.

Issue is respectfully taken with the allegation that the "property of being a lubricant is inherent to the wax disclosed in the prior art as a delaying agent." Although wax maybe a lubricant for molds and other such surfaces, it is otherwise regarded in pharmaceutical technology. In support of this position references are respectfully made to "Biochemistry", second edition, page 295 (copy herewith), which states:

> Waxes are water-insoluble, solid esters of higher fatty acids with long-chain monohydroxylic fatty alcohols or with sterols...They are soft and pliable when warm but hard when cold.

See also "Handbook of Pharmaceutical Excipients", second edition, pages 327, 328, 550 to 561, and 651 (copies herewith), 1994, which confirm:

Paraffin - Ointment base; stiffening agent. (page 327)
Anionic Emulsifying Wax - Emulsifying agent; stiffening agent. (page 550)
Carnauba Wax - Coating agent. (page 552)
Microcrystalline Wax - Coating agent; stiffening agent. (page 554)
Nonionic Emulsifying Wax - Emulsifying agent; stiffening agent. (page 556)
White Wax - Emulsion stabilizer; stiffening agent. (page 558)
Yellow Wax - Emulsion stabilizer; stiffening agent. (page 560)

From the foregoing it is readily apparent that, with regard to pharmaceutical excipients, the noted waxes are not recognized as lubricants.

The fact that Arlacel 165 is a complex of glycerol monostearate and PEG-100 stearate does not mean that it is an acceptable lubricant.

Applicants' claim 22 merely states that its contemplated lubricant includes "a derivative of polyethylene glycol and glycerin"; it does not mean that it includes all derivatives of polyethylene glycol and glycerin. It is limited to a pharmaceutically acceptable lubricant.

Issue is further taken with the allegation that "the patent discloses a composition consisting of somatotropin, a lipid-soluble vitamin and a lubricant" no such composition is found in Kim.

In Kim's Example 1, the ratio is a weight/volume ratio, whereas Applicants' claim 17 is a percentage by weight. The equivalency is not established.

With all due respect, the compositions disclosed by Kim do not meet the limitations of claims 15 to 18, 21 and 27. As Applicants' sole independent claim is in "consists of" terminology, no anticipation whatsoever is provided by any composition disclosed by Kim.

The object of Kim's patent is to provide a slow releasing bioactive composition in order to maintain the biological activities of bioactive polypeptide having short half-life in vivo. On the other hand, the object of the present invention is to provide a somatotropin formulation composition with improved syringeability as well as the sustained release effect of maintaining the activity of somatotropin in vivo. The present invention shows a good syringeability under

cold temperature, an increase in productivity of milk, a decrease in the incidence of mastitis, a decrease injection frequency resulting in reducing the labor and cost for administration and a decrease of animal's pain by administering somatotropin and vitamins in high concentration. Thus, the present invention and Kim's patent, respectively, have different objects and different properties.

The present invention provides a composition comprising somatotropin, at least one of pharmaceutically acceptable lubricant, and at least one lipid-soluble vitamin, which is vitamin A or its derivative or vitamin E or its derivative. On the other hand, Kim discloses a composition comprising a lyophilized mixture including somatotropin, a release-delaying agent, and a tocopherol compound (also, known as vitamin E), wherein said lyophilized mixture is suspended in said tocopherol compound to form a suspension.

In addition, the composition of the present invention has a high concentration of somatotropin. The composition with a high concentration has a high viscosity. Also, the viscosity of vitamin E may be increased at low temperatures. This high viscosity may cause a problem in syringeability of the final formulation of the composition. To settle the problem, the lubricant (as in liquid phase) is applied in the present invention by adding it into the mixture of somatotropin and lipid-soluble vitamins. The lubricant is also used to keep the somatotropin intact in the formulation.

On the other hand, Kim does not need to use a lubricant because of having a low concentration of somatotropin, which means low content of somatotropin. Kim's release-delaying agent is chosen only to slowly release bioactive polypeptide in vivo, that is, the release-delaying agent may be mixed with somatotropin at the same time, and then suspended in a tocopherol compound. Thus, Kim does not provide any constituent to lower the concentration or viscosity of the final solution, and keep the somatotropin intact in the formulation.

A somatotropin formulation in accordance with the present invention is prepared by preparing a somatotropin in powder from by lyophilizing a somatotropin solution alone; mixing the lyophilized somatotropin powder with lipid-soluble vitamins and pharmaceutically acceptable lubricant; and preparing somatotropin formulation in a suspension.

On the other hand, Kim's product is prepared by mixing somatotropin and a release-delaying agent; lyophilizing the mixture; and suspending the lyophilized mixture in a tocopherol

compound to form a suspension.

Kim's release-delaying agent cannot control the viscosity of the final suspension, whereas a lubricant of the present invention can control the viscosity of the final suspension.

Meanwhile, the Examiner indicated that the wax used as a release-delaying agent in Kim's patent is a kind of lubricant. However, as you may know through the documents separately attached hereto, a pharmaceutically acceptable wax such as wax, carnauba wax, paraffin or the like have their melting point in the range of 55 to 102°C, therefore, they are in solid phase at room temperature. Furthermore, these waxes are used mainly as a stiffening agent in many formulations. Accordingly, the intended object to drop concentration or viscosity in a final solution of the present invention cannot be accomplished with wax.

Many of Kim's examples confirm that release-delaying agents do not have the same function as Applicants' lubricant.

In Kim's Examples 1 to 11. Phospatidyl choline (lecithin), a sort of delaying agent, is mixed with bovine somatotropin (bst) bulk solution in a homomixer, and the mixture in an emulsion form is lyophilized to obtain bst-lecithin powder, and the powder is suspended in vitamin E acetate to prepare a somatotropin formulation with a concentration of under 10% of somatotropin.

In Kim's other Examples. Aluminum monostearate, calcium stearate, wax, carnauba wax and paraffin, used as a delaying agent, are mixed with vitamin E acetate, and the viscosity of the mixture is increased, so that the sustained release effect is maximized. But, the syringeability of the final somatotropin formulation is worse, so that the final somatotropin is not useful commercially. Bovine somatotropin is then suspended in said mixture to have the concentration under 10% of somatotropin. This low concentration results in increasing syringeability a little. However, the final somatotropin formulation cannot be easily used in cold areas or in winter under low temperature because the viscosity of vitamin E acetate is increased at low temperature. Moreover, the low concentration needs administration in a large volume of formulation, and the large volume causes inconvenience of administration and more animal pain.

On the contrary, the present invention overcomes those problems. The high concentration of somatotropin lowers the volume of administration, which avoids inconvenience in administration and decreases animal pain. Furthermore, the increased viscosity of vitamin E at

low temperature is overcome by using lubricant.

As mentioned above, Kim's release-delaying agent is different from the lubricant in the present invention. Thus there is no need to account for the amount of the release-delaying agent not being in the range of Applicants' lubricant.

The rejection of claims 15 to 27 "under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 6,497,886" (Breitenbach) is also respectfully traversed. The object of the present invention is to provide a composition comprising somatotropin and vitamins with a decrease of injection frequency, an increase of productivity of milk, a decrease of the incidence of mastitis, and especially improved syringeability. On the other hand, the object of Breitenbach's patent is to provide solvents for pharmaceutical and cosmetic preparations, which have excellent dissolving capacity for the active ingredient used, miscibility with other solvents and good physiological tolerability.

The present invention provides a composition comprising somatotropin, a pharmaceutically acceptable lubricant, and a lipid-soluble vitamin.

On the other hand, Breitenbach's patent provides a pharmaceutical or cosmetic composition comprising at least one 1,3-bis (N-lactamyl) propane as solvent, and active ingredients which can be dissolved in said solvent. The active ingredients can be with or without other conventional vehicles and/or ancillary substances, wherein the conventional vehicles can be water, ethanol, glycerol, polyethylene glycols, hydroxybenzoate (Example 10), PEG-stearate and cetyl palmitate (Example 12), and so on. Breitenbach discloses 77 compounds for concrete examples of active ingredients. Nothing is found in Breitenbach that would render obvious a composition within the scope of any of Applicants' claims.

Particular attention is respectfully directed to the properties of Applicants' claimed products. From a standpoint of patent law, a product and all of its properties are inseperable; they are one and the same thing. The patentability of the product does not depend on the similarity of its structure to that of another product but of the similarity of the former product to the latter. There is no basis in law for ignoring any property in making such a comparison. *In re Papesch*, 137 U.S.P.Q. 43 (CCPA 1963).

To preclude patentability under 35 U.S.C. § 103, there must be some predictability of success in any attempt to combine elements of reference processes. *In re Rinehart*, 189 U.S.P.Q.

143, 148 (CCPA 1976).

Applicants' claimed products have overcome prior deficiencies in the art in a manner which is neither disclosed by nor obvious from anything derivable from Breitenbach.

A somatotropin formulation in accordance with the present invention is a suspension prepared by mixing somatotropin with lipid-soluble vitamin and lubricant. On the other hand, Breitenbach's solution is prepared by dissolving the active ingredient, such as somatotropin, lipid-soluble vitamin or the like in 1,3-bis-(N-lactamyl) propane with or without other conventional vehicles, such as water, ethanol, glycerol, polyethylene glycols, hydroxybenzoate, PEG-stearate and cetyl palmitate, and the like.

Thus, Breitenbach's composition is fully in solution phase and the composition of the present invention is in suspension phase. Syringeability of a suspension according to the present invention is superior to that of Breitenbach's solution.

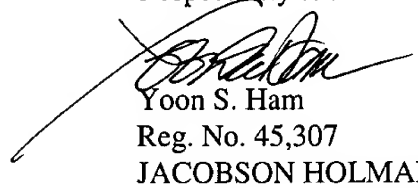
Furthermore, if the solvent, 1,3-bis-(N-lactamyl) propane, is used as a lubricant in the present invention, it can cause a problem in a final extended-release formulation because both somatotropin and lipid-soluble vitamin are fully soluble therein.

The insistence that wax is a natural lubricant is respectfully challenged in the context of Applicants' claims for the previously noted reasons and the accompanying confirming evidence.

The allegation that Applicants' amendment "necessitated the new ground(s) of rejection presented" in Paper No. 9 is also respectfully challenged. Applicants' amendment was virtually only editorial in nature and did not require any new grounds of rejection. Accordingly, the finality of Paper No. 9 is respectfully challenged. Reconsideration of withdrawal of such finality is thus in order and is respectfully solicited in the event that the application is not now in condition for allowance.

Favorable action on the merits and processing this application for allowance are in order and are respectfully solicited.

Respectfully submitted,



Yoon S. Ham
Reg. No. 45,307
JACOBSON HOLMAN, PLLC

The Jenifer Building
400 Seventh Street, N.W.
Washington, D.C. 20004
(202) 638-6666
Attorney Dkt. No.: P67297US0
Date: August 18, 2003